Sustained delivery of low-dose anti-CTLA-4 by genetically engineered encapsulated cells drives tumor response and prolongs survival in a colorectal cancer model

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**ABSTRACT**

Systemic therapy with CTLA-4 blocking antibody (aCTLA4) restores endogenous antitumor immunity and induces remarkable long-term clinical benefits in patients with melanoma. Yet immune-related side effects remain a major hurdle to extend its label to many more types of cancer. Intra- and peritumoral administration of aCTLA4 has recently emerged to optimize its dose/efficacy ratio while preventing its on-target, off-tumor systemic toxicities. Sustained delivery of low-dose aCTLA4 by genetically engineered encapsulated cells (MVX-3) could offer a promising option for cancer treatment addressing the shortcomings of systemic therapy.

**MATERIALS AND METHODS**

**RESULTS**

- **Study Design**
  - D0: MC38 tumor inoculation in hCTLA-4-KI mice
  - D10: Peritumoral implantation of MVX-3 or i.p. injection of ipilimumab (low e4)
  - D17: Sacrifice of satellite mice for organs flow cytometry
  - Sacrifice when mice have a tumor > 1000 mm³ or a high disease score

- **Experimental intervention (MVX-3)**
  - Transplantation of human myeloid cell line (MVX-3)
  - MVX-3 capsules: Encapsulated aCTLA secreting cells
  - Local delivery of aCTLA4

**CONCLUSIONS**

- Peritumoral administration of MVX-3 induced durable complete tumor rejection (2/7) and tumor growth control (4/7) when administered at doses 1’000 times lower than i.p. ipilimumab, whereas rapid tumor growth without any tumor rejection were observed in negative control mice.
- I.p. ipilimumab induced durable complete tumor rejection (9/12), while treatment related toxicities upon dosing led to premature mice termination (3/12).
- MVX-3 was found as equally effective as i.p. ipilimumab in decreasing the proportion of CTLA4+ helper and regulatory T cells in the tumor at Day 7 post treatment.
- Survival was also improved by MVX-3 compared to control. These findings suggest that a sustained, controlled delivery of low-dose aCTLA4 by genetically engineered encapsulated cells could achieve similar therapeutic benefit as the systemic therapy, without the commonly associated severe toxicities. The safety and biological efficacy profile of MVX-3 encourage further preclinical and clinical explorations.